This Month in Genetics

Kathryn B. Garber[1,*]

Reverse Diagnosis of Lynch Syndrome Mutations

Mutations in several mismatch-repair genes cause Lynch syndrome, but not all sequence variation in these genes causes disease. Unfortunately, it can sometimes be difficult to tell in which category a variant should be placed. Once a variant is found in an affected individual, the experiments needed to measure the effect of a single variant on protein function are time consuming and impractical for a diagnostic lab, which means that variants often go unclassified. Drost et al. flipped this approach on its head. They used a cell-culture system to identify critical residues in the mismatch-repair gene *Msh2* so that it might inform the interpretation of variation found in affected individuals. Mouse embryonic stem cells containing a single allele of *Msh2* were mutagenized with ENU, and cells with a second hit in the gene were isolated via selection. Deleterious mutations at a total of 23 amino acid residues were identified, and these were characterized extensively in a series of functional assays. Of these residues, variation at 11 has been reported in individuals suspected of having Lynch syndrome. Although this is most likely not a complete catalog of the critical residues in Msh2, this "reverse diagnosis catalog" of mutations provides another source of data for the interpretation of sequence variation in MSH2, and the same system can be used for cataloging variation in other relevant mismatch-repair genes.

Drost et al. (2013). Proc. Natl. Acad. Sci. USA 110, 9403–9408.

New Database of Conditions Is Based on Clinical Utility of Genetic Diagnosis

As the debate about the return of incidental findings from genomic testing rages on, one issue that is sometimes overlooked is the challenge of picking out the sequence variation that has clinical significance from among the reams of data. To manage this issue, Solomon et al. from the National Human Genome Research Institute constructed a manually curated database of single-gene conditions according to available clinical interventions. They call it the Clinical Genomic Database (CGD). Each entry links to many of the well-known genetic databases, such as OMIM, GeneReviews, and the 1000 Genomes Project, which can be used for further information. As opposed to these other databases, CGD focuses on currently available interventions and their rationale. More than 2,600 genes are already included in the database, and for over half of these, a medical intervention meeting the following criteria is available: (1) the condition caused by mutations in the gene is clinically significant; (2) there is a currently available, potentially beneficial intervention; and (3) genetic diagnosis has an advantage over symptom-based diagnosis. CGD will be regularly updated, and the curators are seeking comments on individual entries from content experts.

Solomon et al. (2013). Proc. Natl. Acad. Sci. USA 110, 9851–9855.

Gene in Prader-Willi Syndrome Critical Region Is Responsible for Precocious Puberty

Estimates suggest that at least one-quarter of cases of precocious puberty are familial, but the underlying genetic explanation is almost always elusive. Mutations in two genes have been reported but are detected in only a very limited number of individuals with early puberty. Expecting autosomal-dominant inheritance, Abreu et al. used an exome-based approach to identify the responsible mutations in 15 families affected by central precocious puberty. In five of the families, they found point mutations in *MKRN3*, an imprinted gene that resides in the Prader-Willi syndrome (PWS) critical region. Consistent with the paternal expression of this gene, mutation carriers were affected only when the mutation was inherited from their fathers. If loss of function of this gene causes precocious puberty, why is this not a hallmark feature of PWS? In fact, precocious puberty has been reported in a small number of PWS cases. Most affected individuals, however, have hypogonadism due to hypothalamic dysfunction, and this is, in fact, a major clinical diagnostic criteria for PWS. Many of these individuals do not spontaneously complete puberty at all, never mind early. Thus, the effects on sexual development of the additional genes deleted in PWS appear to be epistatic to loss of *MKRN3*, possibly because there is a more fundamental defect in hypothalamic function.

Abreu et al. (2013). N. Engl. J. Med. Published online June 5, 2013. http://dx.doi.org/10.1056/NEJMoa1302160.

The Same Somatic Mutation Causes Sturge-Weber Syndrome and Isolated Port-Wine Stains

Port-wine stains of the skin are not uncommon capillary malformations that cause skin discoloration. Generally, they occur in isolation, but, particularly if distributed along the ophthalmic branch of the trigeminal nerve, they can be a part of Sturge-Weber syndrome, in which

[1]Department of Human Genetics, Emory University School of Medicine, Atlanta, GA 30322, USA
*Correspondence: kgarber@genetics.emory.edu
http://dx.doi.org/10.1016/j.ajhg.2013.06.018.

there are also intracranial vascular anomalies that commonly cause epilepsy and glaucoma. Both conditions are thought to result from somatic mutations. To identify the underlying causes, Shirley et al. performed whole-genome sequencing of affected tissues and compared the results to the sequence from unaffected tissues of the same individuals. In *GNAQ*, an identical missense change that activates signaling through the encoded protein was found in affected tissues from the majority of individuals with either condition. Presumably, the timing and location of the mutation during development determines the extent of the phenotype.

Shirley et al. (2013). N. Engl. J. Med. 368, 1971–1979.

Like Mother, Not Like Daughter?

A fundamental idea of biology is that DNA replication generates two identical strands of DNA. How, then, can there be asymmetric segregation of the resulting chromatids during cell division? Adapting a fluorescence in situ hybridization procedure that uses strand-specific probes, Yadlapalli and Yamashita describe this phenomenon in male germline stem cells (GSCs) of *Drosophila*. Although sister chromatids of the autosomes segregate randomly when these cells divide, there is biased segregation for the X and Y chromosomes in that GSCs retain the same sister chromatid 85% of the time. Mutations in components of the centrosome and of the complex that tethers the nucleus to the cytoskeleton randomize chromatid segregation, leading the authors to propose that the individual sister chromatids are recognized in some fashion and that one is tethered to the mother centrosome, which is inherited by GSCs. A clue as to how the chromatids are distinguished is the fact that segregation of sister chromatids is randomized in *dnmt2*-mutant flies. Various crosses with these mutants indicate that DNMT2 confers a heritable but DNA-sequence-independent mark on the sex chromosomes and that this mark is set during gametogenesis of the parents and maintained during embryogenesis. The value of this mark in GSCs remains to be revealed.

Yadlapalli and Yamashita (2013). Nature 498, 251–255.

This Month in Our Sister Journals

Methods for Use of Low-Coverage Sequencing in Association Studies

Particularly in an era of shrinking budgets, one has to be mindful of getting the most bang for the buck from a research-study design. As genome-wide association studies begin to target rare variation instead of common variation as a risk factor for genetic disease, the sample sizes—and money—needed for detecting this variation inflate and quickly go out of reach for most investigators. The lower the frequency of the relevant rare variation, the lower the power to detect it for a given sample size. Methods that aggregate rare variation within a certain region of the genome have been developed for circumventing this issue, but these approaches generally cannot be used with low-coverage, error-prone sequence data. To use just this kind of cheap-to-produce data, Navon et al. developed two methods, called LRT and VST, that use allele counts from sequence data in association tests. Real and simulated data are used for determining the best way to maximize power for a given budget, hopefully bringing these rare-variant studies within reach of more researchers.

Navon et al. (2013). Genetics. Published online May 1, 2013. http://dx.doi.org/10.1534/genetics.113.150169.